Paraneoplastic Cerebellar Degeneration Associated With Ovarian Adenocarcinoma: A Case Report and Review of Literature

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Abstract

Paraneoplastic syndromes are a rare heterogeneous group of disorders that are indicators of the underlying occult malignancy. Subacute cerebellar ataxia in a patient with a known cancer is often due to metastatic invasion or other complications of the cancer, such as infection, coagulopathy, metabolic and nutritional deficits, or side effects of treatment. When tumor- and treatment-related causes have been excluded, the patient is considered to suffer from paraneoplastic cerebellar degeneration (PCD). We report a case of PCD that presented before any evidence of tumor, but early diagnostic workup and clinical vigilance helped us to find the underlying high-grade ovarian adenocarcinoma which was surgically removed later.

Keywords: Adenocarcinoma, anti-Yo antibody, cerebellar ataxia, paraneoplastic

Introduction

Paraneoplastic cerebellar degeneration (PCD) is a collection of neurological disorders resulting from tumor-induced autoimmunity against cerebellar antigens. There are nearly thirty different antibodies (Abs) associated with this condition.[1] Between 90% and 98% of patients with cerebellar ataxia and anti-Yo Abs have a cancer detected, the vast majority of which are pelvic and breast cancers.[2,3] A few cases with lung cancers have been reported, while in male patients, many of the tumors reported were adenocarcinomas of the gastrointestinal system and prostate.[4-6] Given the association with breast and gynecological cancers, females form the vast majority of patients, with <20 cases described in males.[4] The prevalence of anti-Yo PCD, however, is still very low – one study found that only 2.3% of 557 patients with ovarian cancer and 1.6% of 253 patients with breast cancer were positive for the Ab, and only about 12% of those positive for the Ab had PCD.[7] Another case series of 181 patients with ovarian cancers showed that four had elevated anti-Yo titers, but none of them developed symptoms within 2 years of follow-up.[8] Given that anti-Yo PCD accounts for approximately half of all PCDs, it is among the best studied of the paraneoplastic cerebellar syndromes. Still, because of its rarity, the majority of the clinical literature on this topic remains in the form of case series and reports.[9]

Cerebellar degeneration and cancer

Subacute cerebellar ataxia in a patient with a known cancer is often due to metastatic invasion or other complications of the cancer, such as infection, coagulopathy, metabolic and nutritional deficits, or side effects of treatment.[10] When tumor- and treatment-related causes have been excluded, the patient is considered to suffer from PCD. In adult patients who are not known to have a malignancy, subacute cerebellar ataxia may cause a diagnostic challenge, as PCD can precede the presentation of a neoplasm by several months to years.[11]

Brouwer first described PCD in 1919, but the association of cerebellar ataxia and cancer was not recognized until 1938.[12,13]

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Ovarian, lung, and breast cancers and Hodgkin's lymphoma are the neoplasms most commonly associated with PCD.[10] The pathology of PCD is characterized by severe loss of cerebellar Purkinje cells and the presence of inflammatory infiltrates in affected areas of the nervous system.[10] Trotter *et al*. first described auto-Abs reactive with cerebellar Purkinje cells in the serum of a patient with Hodgkin's lymphoma and PCD.[14] Since then, the search for paraneoplastic antineuronal Abs associated with PCD has resulted in the identification of many paraneoplastic Abs and the subsequent cloning of their onconeural target antigens.[15]

Case Report

A 65-year-old, right-handed woman presented to our hospital with complaints of acute-onset and rapidly progressive imbalance while walking and tremulousness of body and limbs for 2 months. She also developed sudden-onset severe throbbing headache, which was partially relieved with analgesics. Her medical and surgical histories were noncontributory. Her social history did not include any alcohol consumption or smoking. Physical examination initially showed slight ataxia on finger to nose and heel to shin on testing. Her gait was broad based and unsteady. Plantar responses were equivocal and she was unable to do tandem walking. The rest of her physical examination was unremarkable, including a negative breast examination.

Diagnostic workup

Her routine blood tests were within normal limits. A lumbar puncture cerebrospinal fluid (CSF) tap was done, but CSF analysis was nonspecific. The chest radiograph was unremarkable. Given the lack of other diagnostic clues for this subacute cerebellar ataxia, a possibility of PCD was raised and followed up with further workup. All the relevant differentials of subacute ataxia in adults were considered, as shown in Table 1.[9] Magnetic resonance imaging (MRI) at the presentation showed clear enhancement of the folia of the cerebellum with diffuse, mild cerebellar atrophy [Figure 1].

Table 1: Differential diagnosis for subacute ataxia in adults

Differential diagnosis for subacute ataxia in adults
Demyelinating diseases such as multiple sclerosis
Systemic autoimmune disorders such as sarcoidosis, Behcet's disease, lupus
Alcohol abuse, Wernicke's syndrome, Vitamin E and B12 deficiencies
Medication toxicities, for example, phenytoin
Miller–Fisher variant of Guillain–Barre syndrome
Steroid-responsive encephalopathy associated with thyroid disease
Anti-GAD antibody-associated ataxia
Gluten ataxia, celiac disease
Atypical infections: Progressive multifocal leukoencephalopathy, prion disease
Paraneoplastic cerebellar degeneration

GAD=Glutamic acid decarboxylase

Extensive diagnostic workup was done to find tumor in the body. Fludeoxyglucose-positron emission tomography MRI of the whole body was done which revealed left tubo-ovarian mass with avid enlarged retroperitoneal lymph nodes and mildly avid endometrial polyp [Figure 2]. Fine-needle aspiration cytology of left tubo-ovarian mass was done, which showed features suggestive of high-grade, Stage III A1 (T1, N1, M0) serous adenocarcinoma. Her serum was positive for anti-Purkinje cell auto-Abs. The result of Western blot analysis was consistent with anti-Yo Ab, one of the anti-Purkinje cell Abs. A diagnosis of PCD was made.

She underwent laparotomy and subsequent total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic washes. Postoperatively, the patient was started on treatment with carboplatin and paclitaxel. On the second postoperative day, the patient was started on intravenous immunoglobulin (IVIG) for the management of PCD. IVIG was given for a total duration of 5 days. The patient responded partially to treatment and made modest improvement in her balance during transfers and ambulation at the time of discharge.

Discussion and Literature Review

Paraneoplastic syndromes (PNSs) are a rare heterogeneous group of disorders that are indicators of the underlying occult malignancy. It is a primary neurological syndrome that is triggered by an erroneous immune-mediated attack on the nervous system antigens, originally directed against the tumor itself.[16] Any part of the brain could be involved in PNS, and isolated neurologic manifestations appear months or years before the detection of primary malignancy. It occurs before the presenting complaints of neoplasm in up to 65%–80% of cases, and so it can help in the early diagnosis of tumor.[16-18] When diagnosed earlier and in more favorable stages, the tumor can be treated with more chances of cure in the patient. Prognosis of patients with cancer presenting with PNS is better compared to those without PNS

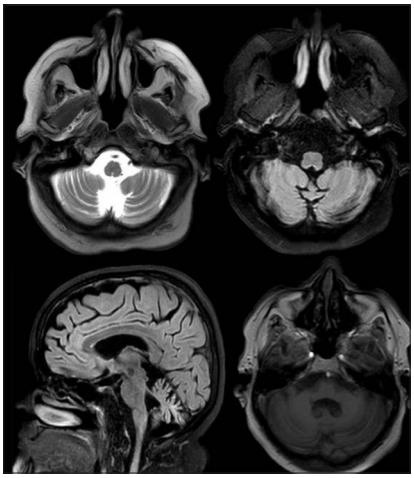

Figure 1: Magnetic resonance imaging at presentation showing clear enhancement of the folia of the cerebellum with diffuse cerebellar atrophy

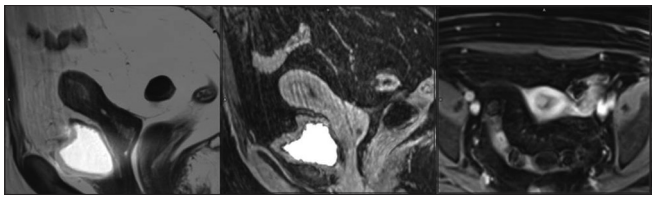

Figure 2: Fludeoxyglucose-positron emission tomography magnetic resonance imaging showing fludeoxyglucose avid left tubo-ovarian mass

due to detection of cancer at early stage, although the prognosis may be poor due to severe neurological morbidity.[19]

The clinical course in patients with different Abs varies.[20] Patients with anti-Yo Ab-positive PCD are often severely incapacitated; however, the neurologic disability is rarely the cause of death.[21-23] By contrast, the neurologic disorders in patients with anti-Hu Abs can result in the death of the patients.[24,25] In addition, anti-Yo-positive patients only have restrictive cerebellar dysfunction, whereas the patients carrying anti-Hu Abs often present with a more widespread neurologic disorder called paraneoplastic encephalomyelopathy and sensory neuronopathy.[24,25] Some anti-Hu-positive patients who have isolated cerebellar disorders may also develop Lambert–Eaton myasthenic syndrome.[26,27] Pathologic features also differ in PCD associated with different antineuronal Abs. Anti-Yo Abs interact with cellular antigens of Purkinje cells. Complete loss of Purkinje cells with mild or no inflammatory infiltrates in the cerebellum is characteristic.[21-23] In contrast, anti-Hu Abs bind to the nucleoproteins of neurons with accompanying extensive inflammatory infiltrates and neuronal degeneration in the nervous system.[25]

Around 50% of subacute cerebellar ataxia occurs due to nonparaneoplastic causes.[16] Subacute cerebellar syndrome can also occur due to vitamin deficiency (B1, B12, E, or folic acid), in alcoholics, due to infectious causes (varicella zoster virus, Epstein–Barr virus, Whipple's disease, and Creutzfeldt–Jakob disease), due to immune-mediated nonparaneoplastic causes (gluten-sensitive enteropathy), or due to hereditary causes which need to be considered in differential diagnosis.[28] Since based on clinical features one cannot reliably distinguish between these causes, patients of subacute cerebellar ataxia of uncertain cause should be screened for onconeural Abs.

Paraneoplastic Abs that are associated with PCD are anti-Yo, anti-Hu, anti-Tr, anti-Ri, anti-CV2, anti P/Q type voltage-gated calcium channel, amphiphysin, anti-Ma2, and anti-GluR1.[28] These Abs have great diagnostic as well as some prognostic value.[29] The presence of well-characterized paraneoplastic Abs such as anti-Hu, anti-Yo, or anti-Tr in a case of subacute cerebellar ataxia makes it a definite case of PCD even in the absence of cancer.[2] It also helps in guiding the investigation of occult malignancy. Anti-Yo Ab which is the most common Ab in patients with PCD is commonly associated with ovary, breast, or other gynecological cancers. Likewise, the second most common Ab in PCD, anti-Hu Ab, is associated with small-cell lung cancer in more than 85% cases.[28] In our patient, it was the anti-Yo Ab which was found to be positive which in turn led us to extensive diagnostic workup for the underlying tumor, proving its diagnostic value in cases of cerebellar degeneration. Subsequently, it was the high-grade ovarian adenocarcinoma which was recognized as the cause for this paraneoplastic presentation.

Since anti-Yo and anti-Hu auto-Abs are relatively specific for a narrow range of cancers, they can be very useful tumor markers for the underlying cancers. The key is to have a high index of suspicion when a patient presents with subacutely evolving cerebellar dysfunction. When PCD is suspected, it should prompt serum analysis to recover the antineuronal Abs. If serum is positive for anti-Purkinje cells Abs, Western blot analysis is usually pursued to reveal the precise identity of the Abs. The reaction of serum with both CDR62 and CDR34 suggests positive anti-Yo Abs in the patient's serum. Patients with positive anti-Yo Abs should be evaluated for occult ovarian or breast cancer.[30]

Successful treatment of PCD, in general, has so far been limited.[31] In a few cases, significant resolution of the PNS was achieved after treatment of the underlying cancer. Plasmapheresis and immunosuppression have usually not been effective. However, it was reported recently that a patient with recurrent ovarian cancer and PCD had significant improvement of cerebellar function with treatment using plasmapheresis and immunoglobulin.[32] The different response to treatment may be due to the stages of neurologic damage.[30] Our patient received IVIG therapy and showed partial improvement in her cerebellar symptoms.

Conclusion

- The majority of cases of tumor occurrence are preceded by months or even years by cerebellar signs; in this case report, we observed that PCD emerged even before any manifestations of the primary ovarian tumor
- Failure to pick up the early warning signs of PCD due to various reasons can land the patients into more advanced stages that are not amenable to curative therapy. A high degree of suspicion has to be practiced in such cases of cerebellar degeneration, in order to get to the underlying tumor
- Despite anecdotal case reports revealing neurological improvement with various combinations of treatment, there remains a requirement for greater efficacy in therapy for PCD
- Further investigations on the pathogenesis of PCD are required to identify more effective therapies, which are able to stabilize or reverse the neurological symptoms.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jarius S, Wildemann B. 'Medusa-head ataxia': The expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 1: Anti-mGluR1, anti-homer-3, anti-sj/ITPR1 and anti-CARP VIII. J Neuroinflammation 2015;12:166.
2. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, *et al.* Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004;75:1135-40.
3. Sadeghian H, Vernino S. Progress in the management of paraneoplastic neurological disorders. Ther Adv Neurol Disord 2010;3:43-52.
4. Hasadsri L, Lee J, Wang BH, Yekkirala L, Wang M. Anti-Yo associated paraneoplastic cerebellar degeneration in a man with large cell cancer of the lung. Case Rep Neurol Med 2013;2013:725936.
5. Meglic B, Graus F, Grad A. Anti-Yo-associated paraneoplastic cerebellar degeneration in a man with gastric adenocarcinoma. J Neurol Sci 2001;185:135-8.
6. Sutton IJ, Fursdon Davis CJ, Esiri MM, Hughes S, Amyes ER, Vincent A, *et al.* Anti-Yo antibodies and cerebellar degeneration in a man with adenocarcinoma of the esophagus. Ann Neurol 2001;49:253-7.
7. Monstad SE, Storstein A, Dørum A, Knudsen A, Lønning PE, Salvesen HB, *et al.* Yo antibodies in ovarian and breast cancer patients detected by a sensitive immunoprecipitation technique. Clin Exp Immunol 2006;144:53-8.
8. Drlicek M, Bianchi G, Bogliun G, Casati B, Grisold W, Kolig C, *et al.* Antibodies of the anti-Yo and anti-ri type in the absence of paraneoplastic neurological syndromes: A long-term survey of ovarian cancer patients. J Neurol 1997;244:85-9.
9. Venkatraman A, Opal P. Paraneoplastic cerebellar degeneration with anti-Yo antibodies – A review. Ann Clin Transl Neurol 2016;3:655-63.
10. Henson RA, Urich H. Cancer and the Nervous System. Oxford: Blackwell Scientific; 1982.
11. Posner JB. Paraneoplastic syndromes. In: Neurologic Complications of Cancer. Philadelphia: F.A. Davis; 1995. p. 353-85.
12. Brouwer B. Beitrag zur kenntnis der chronischen diffusen kleinhirnerkrankungen. Neurol Centralbl 1919;38:674-82.
13. Brouwer B, Biemond A. The parenchymatous affections of the cerebellum and their significance from the point of view of the anatomy and the physiology of this organ. J Belge Neurol Psychiat 1938;38:691-757.
14. Trotter JL, Hendin BA, Osterland CK. Cerebellar degeneration with Hodgkin disease. An immunological study. Arch Neurol 1976;33:660-1.
15. Shams'ili S, Grefkens J, de Leeuw B, van den Bent M, Hooijkaas H, van der Holt B, *et al.* Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: Analysis of 50 patients. Brain 2003;126:1409-18.
16. Honnorat J, Antoine JC. Paraneoplastic neurological syndromes. Orphanet J Rare Dis 2007;2:22.
17. Giometto B, Grisold W, Vitaliani R, Graus F, Honnorat J, Bertolini G, *et al.* Paraneoplastic neurologic syndrome in the PNS Euronetwork database: A European study from 20 centers. Arch Neurol 2010;67:330-5.
18. Rojas I, Graus F, Keime-Guibert F, Reñé R, Delattre JY, Ramón JM, *et al.* Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology 2000;55:713-5.
19. Pelosof LC, Gerber DE. Paraneoplastic syndromes: An approach to diagnosis and treatment. Mayo Clin Proc 2010;85:838-54.
20. Mason WP, Dalmau J, Curtin JP, Posner JB. Normalization of the tumor marker CA-125 after oophorectomy in a patient with paraneoplastic cerebellar degeneration without detectable cancer. Gynecol Oncol 1997;65:173-6.
21. Peterson K, Rosenblum MK, Kotanides H, Posner JB. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. Neurology 1992;42:1931-7.
22. Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA. Gynecologic cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited in metastatic volume. Mayo Clin Proc 1990;65:1558-63.
23. Verschuuren J, Chuang L, Rosenblum MK, Lieberman F, Pryor A, Posner JB, *et al.* Inflammatory infiltrates and complete absence of Purkinje cells in anti-Yo-associated paraneoplastic cerebellar degeneration. Acta Neuropathol 1996;91:519-25.
24. Graus F, Elkon KB, Lloberes P, Ribalta T, Torres A, Ussetti P, *et al.* Neuronal antinuclear antibody (anti-hu) in paraneoplastic encephalomyelitis simulating acute polyneuritis. Acta Neurol Scand 1987;75:249-52.
25. Anderson NE, Rosenblum MK, Graus F, Wiley RG, Posner JB. Autoantibodies in paraneoplastic syndromes associated with small-cell lung cancer. Neurology 1988;38:1391-8.
26. Clouston PD, Saper CB, Arbizu T, Johnston I, Lang B, Newsom-Davis J, *et al.* Paraneoplastic cerebellar degeneration. III. Cerebellar degeneration, cancer, and the Lambert-Eaton myasthenic syndrome. Neurology 1992;42:1944-50.
27. Motomura M, Johnston I, Lang B, Vincent A, Newsom-Davis J. An improved diagnostic assay for Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry 1995;58:85-7.
28. Leypoldt F, Wandinger KP. Paraneoplastic neurological syndromes. Clin Exp Immunol 2014;175:336-48.
29. Voltz R, Graus F. Diagnosis and treatment of paraneoplastic neurological disorders. Onkologie 2004;27:253-8.
30. Liu S, Tunkel R, Lachmann E, Nagler W. Paraneoplastic cerebellar degeneration as the first evidence of cancer: A case report. Arch Phys Med Rehabil 2000;81:834-6.
31. Posner JB. Paraneoplastic syndromes. Neurol Clin 1991;9:919-36.
32. David YB, Warner E, Levitan M, Sutton DM, Malkin MG, Dalmau JO, *et al.* Autoimmune paraneoplastic cerebellar degeneration in ovarian carcinoma patients treated with plasmapheresis and immunoglobulin. A case report. Cancer 1996;78:2153-6.